A frequently asked question in clinical pathology is why must statin drugs be dosed in the evening rather than in the morning? The answer is that the liver manufactures more cholesterol in the evening than in morning. Thus, the efficacy of statins is remarkably diminished when the drugs are not dosed at the correct time.

Many biologic phenomena display cyclic variation or rhythmicity, operating according to a ‘biologic timekeeper’. These biologic rhythms are observed as adaptive adjustments to cyclic environmental changes occurring over the course of the day, a month, or a season. Differences in physiology according to the time of day, time of month, time of year, or even the period in one’s life encompass the discipline of chronobiology. The exposure of healthcare providers to the field of chronobiology has been limited.

The endocrine system provides many examples illustrating chronobiology. It is the monthly alteration in hormones that initiates menses. The timing of puberty provides another example. Some components of the endocrine system follow a diurnal pattern of activity.

There are a number of hormones that are secreted in the morning, including cortisol, catecholamines, plasma renin, aldosterone, and angiotensin. In contrast, gastric acid, growth hormone, prolactin, melatonin, follicle-stimulating hormone, luteinizing hormone, and adreno-corticotrophic hormone (ACTH) peak in the evening or during sleep. There are consequences to the circadian changes in these hormones. For instance, the increase in catecholamines in the morning promotes platelet aggregation. This is especially important since fibrinogen also increases, and the body’s own endogenous t-PA decreases, promoting a procoagulant state with increased blood viscosity.

Ambulatory blood pressure has provided insight into the change in blood pressure and heart rate throughout the day. The difference between normotensive and hypertensive patients is the level of blood pressure throughout the day. The peak blood pressure is between 6 am and noon. With activation of the sympathetic nervous system prior to awakening, blood pressure begins to increase. Heart rate also increases.

These changes in blood pressure parallel the morning activation in catecholamines, renin, and angiotensin. Activity and sleep influence the level of blood pressure throughout the day. Between midnight and 6 am, blood pressure is generally lowest. Individuals who work from midnight to 8 am have their lowest blood pressure during their sleep period. Patients with autonomic dysfunction have their lowest blood pressure during standing and highest blood pressure when supine.

Normally, blood pressure declines 10% to 20% from the activity period to the sleep period. Patients with less than a 10% reduction in daytime blood pressure are referred to as ‘non-dippers’. Research suggests that a blunted nocturnal decline in blood pressure may be due to diminished sodium excretory capacity, alteration in the autonomic nervous system, or other factors. In addition, non-dippers are more likely to have a secondary cause of hypertension. Endocrine causes include diabetes mellitus, pheochromocytoma, primary aldosteronism, licorice intoxication, Cushing’s syndrome, and high-dose corticosteroids.

Other causes include autonomic dysfunction, renal failure, obstructive sleep apnea, cardiac transplantation, pre-eclampsia and eclampsia. Target organ damage appears to be more common as a consequence.

Epidemiologic studies document that these individuals are at a greater risk of left ventricular hypertrophy, renal disease, and cardiovascular events. Another group is classified as ‘extreme dippers’ – individuals whose blood pressure declines excessively (>20%) during sleep. These individuals appear to be at an increased risk of blindness (anterior ischemic optic neuropathy) and stroke. Unfortunately, the determination of non-dippers and extreme dippers is confounded by poor repeatability using ambulatory blood pressure monitoring.
Chronopathology refers to the study of biological rhythms in disease processes in morbid and mortal events. Healthcare providers understand that certain diseases occur at specific times of the day. For instance, heart failure exacerbation or esophageal reflux is more likely to be present at night. Careful analysis of trials has documented that myocardial infarction (MI), stroke, ventricular ectopy, and sudden cardiac death occur between 6 am and noon. The risk of myocardial infarction is 40% higher, the risk of cardiac death is 29% higher, and the risk of stroke is 49% higher than that expected to occur by chance. Also, aortic dissection is more common in the morning.

The explanation for the higher rate of cardiovascular events is explained by multiple factors. Vasoconstriction increases with higher levels of circulating catecholamines. Blood pressure and heart rate are higher, increasing shear forces in blood vessels and myocardial oxygen consumption. This creates an environment for plaque rupture. Once plaque rupture occurs, whether in coronary arteries or in other vascular beds, thrombosis occurs in the early morning procoagulant milieu, resulting in a clinical event. Thus, insight into chronobiology and chronopathology has given birth to chronotherapeutics.

Chronotherapeutics is the purposeful alteration of a drug level to match rhythms in order to optimize therapeutic outcomes and minimize side effects. While these concepts have been used in the treatment of peptic ulcer disease, lipids, and asthma for many years, it is a novel concept for cardiovascular diseases. For instance, the goal of this therapy has been to control blood pressure for a 24-hour period.

The paradigm shift of chronotherapeutics is the dosing of medications at 10 pm with novel drug delivery systems to provide additional blood pressure and lower heart rate during the vulnerable period of 6 am to noon. Some healthcare providers believe that dosing any drug at night will achieve that goal, but that concept is flawed since there may be differences in pharmacokinetics and pharmacodynamics depending on when the drug is given. This is explained by differences of gastrointestinal motility, pH, absorption, and bioavailability.

Currently, there are four antihypertensive medications that are chronotherapeutic medications using verapamil (Covera HS, Verelan PM), diltiazem (Cardizem LA), and propranolol (InnoPran XL), and there are likely to be more products available as understanding of chronobiology expands.

**Glossary of Terms**

**Medical Chronobiology**
Study of biological rhythms and their underlying mechanisms.

**Chronopathology**
Study of biological rhythms in disease processes and morbid and mortal events.

**Chronotherapeutics**
Purposeful alteration of drug level to match biological rhythms in order to optimize therapeutic outcomes and minimize side effects.

**Chronopharmacology**
Biological rhythm influences on the effects of medications.

**Chronopharmacokinetics**
Study of biological rhythm effects on the absorption, distribution, and elimination of medications.

**Circadian**
Relating to biological variations or rhythms with a cycle of about 24 hours.
Treat your high-risk patients

• More than two out of every five African-Americans have high blood pressure. That’s a higher percentage than any other group in the world.¹

at the time of highest risk.

• More cardiac events take place in the morning than any other time of day.²

• Reduction of morning blood pressure with Verelan® PM Monotherapy was significant in African-Americans.³,⁴
• Provides 24-hour blood pressure control.
• Almost half of the patients on diabetic medication achieved study target BP (140/90 mmHg) with Verelan PM monotherapy.

CHRONO Trial: Multicenter open-label, forced titration (200 mg to 400 mg) study of Verelan® PM with 2,556 hypertensive patients. Four-week treatment period per dose up to a maximum 12 weeks.⁴

* Target = SBP<140 mm Hg and DBP<90 mm Hg at last visit

Clinical significance of reducing the early-morning rise in BP has not been established.

Verelan® PM is contraindicated in patients with severe left ventricular dysfunction, sick sinus syndrome, atrial flutter or fibrillation and an accessory bypass tract, 2° or 3° AV block, and hypotension.

Headache, constipation, peripheral edema and dizziness were among the most common side effects.

PLEASE SEE THE FOLLOWING PAGE FOR A BRIEF SUMMARY OF PRESCRIBING INFORMATION.
Four Dosing Options

The following is a Brief Summary. For complete prescribing information, see package insert.

INDICATIONS AND USAGE
Verelan PM is indicated for the treatment of: (See CLINICAL PHARMACOLOGY)

CONTRAINDICATIONS
Verelan is contraindicated in: (See WARNINGS)

1. Severe left ventricular dysfunction (See WARNINGS)
2. Hypotension (less than 80 mm Hg systolic or hypodynamic) cardiac shock
3. Sick sinus syndrome (or patients with a functioning atri

4. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndrome) (See WARNINGS)

5. Patients with known hypersensitivity to Verelan HCl

WARNINGS
Heart Failure: Verelan has a negative inotropic effect which, in most patients, is compensated by an afterload reduction (decreased systemic vascular resistance) without a net improvement of ventricular performance. In previous clinical experience with 4,595 patients immediately prior to release of Verelan, 8.7% (1,051) developed congestive heart failure or edema. Verelan should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction less than 30%, or evidence of severe cardiac failure) and in patients with any degree of systolic dysfunction who are receiving a beta-adrenergic blocker (See Drug Interactions). Patients with mild ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before Verelan treatment is commenced (See PRECAUTIONS, Drug Interactions, Digitalis). Hypotension: Occasionally, the pharmacologic action of Verelan may produce a decrease in blood pressure which may result in dizziness or syncope. The hypotensive effect observed in 4,594 patients enrolled in clinical trials was 2.5%. In hypertensive patients, decreases in blood pressure below normal levels were observed in 6.8%. Table testing (0.6°) was unable to induce orthostatic hypotension. In clinical studies of Verelan PM, 1.7% of the patients developed significant hypotension. Elevated liver enzynes: Elevations of transaminases with and without a history of liver disease or a decline in baseline liver function in patients receiving Verelan is therefore prudent. Accessory bypass tract (Wolff-Parkinson-White or Lown-Ganong-Levine syndrome) (See WARNINGS).

Some patients with accessory bypass tracts (Wolff-Parkinson-White syndrome) and normal cardiac function have undergone increased antegrade conduction across the accessory pathway bypassing the AV node, resulting in very rapid ventricular rates in patients with atrial fibrillation or flutter. Although this risk of occurring with our experience of Verelan has not been established, such patients receiving oral verapamil may be at risk in using this in patients susceptible to pre-excitation syndromes. Cardiac arrhythmias have been reported in patients with accessory pathways following effective AV node block by Verelan. Antegrade block. The effect of Verelan on AV conduction and the SA node may lead to atrioventricular block at elevated plasma levels of verapamil. Concomitant administration of quinidine (See Interactions, Digitalis) resulting in elevated blood ethanol concentrations that may prolong the intoxicating effects of alcohol. The clearance of paclitaxel.

Levels. The absorption of verapamil can be reduced by the cyclophosphamide, oncovin, procarbazine, prednisone (COPP) and Vinca alkaloids. Patients with paroxysmal and/or chronic atrial flutter or atrial fibrillation and a coexisting accessory AV pathway have developed

It has been reported that verapamil decreases neuromuscular transmission in patients with

Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium and atracurium. About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Until further data are available, verapamil should be

pressure below normal levels which may result in dizziness or symptomatic hypotension. The incidence of hypotension

Focal ventricular pacemaker). Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndrome) (See WARNINGS). Some patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndrome) (See WARNINGS)

Hypotension 2.5%

In previous experience with other formulations of Verelan (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible

3. Prevention of acute and maintenance treatment of angina pectoris in patients with a history of angina pectoris (See CLINICAL PHARMACOLOGY)

Fenpropinoxal) (9 mg/kg/day) were administered in developing toxic effects on the heart (e.g., atrioventricular dissociation, chest pain, myocardial infarction,

Telithromycin, the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

Sex in men and women of healthy volunteers; clearance of verapamil was either reduced or unchanged. The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance

Other: Nitrates: Nitroglycerin may increase serum levels of cyclosporine. Telithromycin: Verapamil may inhibit the clearance and increase the plasma levels of Telithromycin. Use of Verelan PM should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction less than 30%), or evidence of severe cardiac failure, because of the possible increased risk of cardiovascular reflex tachycardia and/or increased ventricular rate. These adverse effects have not been assessed in patients with chronic obstructive pulmonary disease. Verapamil can also have effects which may result in increased sodium and fluid retention. The combination of

Concomitant administration of quinidine (See Interactions, Digitalis) resulting in elevated blood ethanol concentrations that may prolong the intoxicating effects of alcohol. The clearance of paclitaxel.

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